In vertebrate embryos, commissural axons extend toward and across the floor plate (FP), an intermediate target located at the ventral midline (VM) of the spinal cord. After decussating, many of these axons initially turn into the longitudinal plane and, subsequently, project away from the VM along a complex path. FP contact is thought to alter the responsiveness of commissural axons to midline-associated cues so that they can exit the FP and adopt new trajectories on the contralateral side of the VM. Here, we demonstrate that a significant number of decussated axons elaborate wild-type-like projections even in cultured, FP-excised spinal cord preparations and in the spinal cords of gli2-deficient, FP-lacking mice. Consistent with a role for chemorepulsive Slit proteins in driving commissural axons out of the VM and into longitudinal tracts, slit1–3 mRNA is expressed within the ventral ventricular zone and Slit receptors Robo1/2 are selectively expressed on longitudinal axons in gli2 homozygous embryos. Supporting an active role for Robo–Slit signaling, in the absence of FP contact, blocking Robo–Slit interactions in spinal cord explants derived from gli2 null embryos prevents commissural axons from leaving the VM. Together, these findings show that, at least for a subset of commissural axons, Robo–Slit interactions but not FP contact are required for the proper elaboration of their contralateral projections. Funding: NIH (R01 NS 38505) and NYS SCIRB (C018615).

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A combination of ephrin-As and neural activity is required for visual system mapping

David Feldheim [1], Cory Pfeiffenberger [1], Jianhua Cang [2], Michael Stryker [2]
[1] *UC Santa Cruz, CA, USA*
[2] *UC San Francisco, CA, USA*

Visual information is processed in multiple areas of the mammalian brain, most notably the superior colliculus (SC) in the midbrain, the dorsal lateral geniculate nucleus (dLGN) in the thalamus, and the primary visual areas of the cortex (V1). All of these areas receive inputs that are topographic in nature. Topographic maps are the general rule of nervous system connections and are thought to keep the spatial information of a stimulus intact as it is transferred from one brain region to another. Here, I will share our work on the study of how topographic maps develop in each of these visual regions. We have analyzed the topographic maps of each of these regions in various populations of mice: ephrin-A mutant mice, mice defective in correlated retinal activity (mice mutant in the _2 subunit of the nACh receptor), and mice defective for both ephrin-As and correlated neural activity. We analyzed the nature of the visual connections in these mice both anatomically, using axon tracing techniques, and functionally, using intrinsic optical imaging. We find that both ephrin-As and _2 are required for topographic mapping to all visual structures, but that the relative contribution of each is different between the SC and V1. The analysis of these mice leads us to present a model whereby a combination of topographic mapping molecules and neural-activity-dependent events acts together to create the stereotypical connectivity patterns in the primary visual system.

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Molecular basis for pituitary dysfunction: Comparison of Prop1 and Pit1 mutant mice

Luciani Carvalho, Robert D. Ward, Michelle L. Brinkmeier, Mary Anne Potok, Amanda H. Vesper, Sally A. Camper
Department of Human Genetics, University of Michigan, Ann Arbor, MI, USA

Mutations in the transcription factors PROP1 and PIT1 cause multiple pituitary hormone deficiencies in humans and mice. During normal mouse development, the cells that line the lumen of Rathke's pouch are densely packed and actively proliferating. Between E12.5 and E14.5, these cells delaminate and migrate from the lumen to the anterior lobe in a process similar to an epithelial to mesenchymal transition. In Prop1 mutants, this process fails, vascular development is poor, and after birth reduced cell proliferation and elevated apoptosis are apparent. In contrast, the pituitaries of Pit1 mutants appear normal throughout fetal development, and there is no evidence of delayed vascularization. This comparative study suggests that Prop1 has numerous downstream targets besides Pit1, and identification of those genes will define the molecular basis for pituitary cell migration and vascularization. Differential gene expression analysis revealed several genes, including Hesx1, Tle3, and Notch2, whose expression is altered in Prop1, but not Pit1 mutants. We are in the process of testing the functional consequences of misexpression of these and other genes in transgenic mice and cell cultures. In summary, Prop1 and Pit1 mutant mice are excellent tools for dissecting the molecular basis for pituitary dysfunction and understanding the genetic control of pituitary organ development.

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Regulation of axon fasciculation by Sema3D

Mary C. Halloran, Marc A. Wolman
University of Wisconsin, USA

During neural development, axons often navigate their pathways by fasciculating along particular axon tracts. We are investigating mechanisms of axon-axon interactions and fasciculation in one of the earliest developing tracts in the zebrafish brain, the medial longitudinal fasciculus (MLF). Neurons in the bilateral midbrain nuclei of the MLF (nucMLF) extend axons caudally that adhere to one another and grow as a fascicle into the spinal cord. A semaphorin, Sema3D, is expressed rostral to the nucMLF and in the ventral midline